APPENDIX 1:
SAFETY IN STUDY AV019 (KAISER STUDY)

Study AV019: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety of Frozen FluMist in Healthy Children and Adolescents

Primary Objective:

- To estimate the rates of all medically-attended events (MAEs), including Serious Adverse Events (SAEs) and selected groups of MAEs, following the administration of FluMist compared to the rates following the administration of placebo.

Study Design

Study AV019 was a randomized, double-blind, placebo-controlled trial designed to evaluate the safety of FluMist in healthy children and adolescents. Eligible participants were randomly assigned in a 2:1 fashion to receive FluMist or placebo. Participants less than nine years of age were to receive two doses of FluMist or placebo and participants greater than or equal to nine years of age were to receive one dose. Dose One was administered on Study Day 0 and Dose Two (for participants less than nine years of age) was to be administered 28 days to 42 days later. The goal of this trial was to enroll up to a maximum of 15,000 children prior to the influenza outbreak period.

All participants were members of the Kaiser Permanente (KP) health plan (a closed system healthcare provider). Therefore, the primary method for ascertaining safety outcomes was extraction of MAEs from the KP computerized health care utilization databases for hospitalizations, emergency department (ED) visits, and clinic visits. MAEs were analyzed individually and within four pre-specified grouped diagnoses. The pre-specified grouped diagnoses were selected to capture illness syndromes that have been reported to occur in association with wild-type influenza infection and theoretically might occur after administration of FluMist. These diagnoses included acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza.

Duration of Follow-up

MAEs and SAEs occurring within 42 days after the last dose of study vaccine were collected from the KP computerized databases.

Statistical Methods

A binomial analysis of participant-incidence of MAEs within 42 days of vaccination was performed. Event rates by treatment group, relative risks (rate in FluMist recipients divided by

rate in placebo recipients), and exact, two-sided 90% mid-probability binomial confidence intervals, adjusted for follow-up time, were constructed. A significantly increased risk among FluMist recipients was indicated by a lower bound of the confidence interval > 1, and a significantly decreased risk among FluMist recipients was indicated by an upper bound of the confidence interval < 1. The binomial analysis was a participant-oriented approach: multiple encounters for the same MAE experienced by a given participant were counted only once.

Statistical analysis was performed for each reported MAE diagnosis by each of three utilization settings: the hospital; the outpatient clinic; and the emergency department (ED). Analyses were also performed across utilization settings (hospital, outpatient clinic, and ED combined) for the MAEs that comprised each of the four pre-specified grouped diagnoses (acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza). All analyses were performed stratified by age group (9–17 years, 1–8 years, 18–35 months, 12–17 months) and dose (after Dose One, after Dose Two and after all doses combined, where appropriate).

Approximately 1,500 statistical comparisons were performed in this analysis without adjustment for multiple comparisons. Therefore, there was a high likelihood of observing significant outcomes due to chance alone.

Results

Of the 9,689 evaluable participants, 5,637 (58%) were 1–8 years of age and 4,052 (42%) were 9–17 years of age at entry (Table 1). Six thousand four hundred seventy-three (67%) participants received FluMist and 3,216 (33%) received placebo.

Table 1
Enrollment by Age and Treatment Group for the Evaluable Participants in Study AV019

Age in Years	Treatment Group		Total N (%)
	FluMist n (%)	Placebo n (%)	
1–8	3769 (39)	1868 (19)	5637 (58)
9–17	2704 (28)	1348 (14)	4052 (42)
Total	6473 (67)	3216 (33)	9689 (100)

Twenty SAEs were reported (13 in FluMist recipients and seven in placebo recipients; rate=0.2% which is consistent with the 2:1 randomization), and none were considered related to

FluMist. The frequency of MAEs within 42 days of vaccination as measured by medical utilization in the different utilization settings was similar in the two treatment groups, and ranged from 0.5–0.6% in the hospital, 2.9–3.2% in the ED, and 35.6–37.0% in the clinic. For the pre-specified grouped diagnoses (acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza), no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses, and age groups. In fact, acute respiratory tract events were decreased for FluMist recipients in this combined analysis, and selected respiratory tract illnesses of special interest that were part of acute respiratory tract events—pneumonia, bronchitis, bronchiolitis, and croup—were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection events occurred. The rare events potentially related to influenza that occurred were seizure(s), febrile seizures, and epilepsy, and none were associated with increased risk in FluMist recipients. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or other influenza-associated rare disorders occurred.

A total of 170 individual MAE diagnostic categories were reported in study participants. In at least one analysis, a similar number of these individual MAE categories were associated with significantly increased risk (n=14) (Table 2) as were associated with significantly decreased risk (n=21) (Table 3) in FluMist recipients.

Table 2
MAEs with Significantly Increased Risk

MAE	Setting
Abdominal Pain	ED
Adenitis/adenopathy	Clinic
Asthma	Clinic and Combined
Otitis Media with Effusion	Clinic
Musculoskeletal Pain	Clinic
URI	ED and Combined
Benign Lesion	Clinic
Elective Procedure	Clinic
Enuresis	Clinic
Otitis Externa	Clinic
Seborrhea	Clinic
Speech Delay	Clinic
UTI	Clinic
Warts	Clinic

Of the 14 MAE categories associated with increased risk, a biologically plausible association with FluMist was considered for six: upper respiratory infection (URI), musculoskeletal pain, asthma, abdominal pain, otitis media with effusion (OME), and adenitis/adenopathy. Based on an assessment of the number and types of analyses associated with increased risk and on the presence or absence of temporal clustering in the post-vaccination period, a cause and effect relationship cannot be excluded for FluMist and URI, and, in children 18 to 35 months of age, for musculoskeletal pain and for asthma.

MAEs Associated with Decreased Risk in FluMist Recipients

Of the 21 individual MAEs associated with statistically significantly decreased risk in FluMist recipients, a biological association with receipt of FluMist was considered implausible for 11 (attention deficit disorder [ADD], behavioral disorder, constipation, contact dermatitis, eczema, gingivitis, gynecologic disorder, migraine, thrush, trauma, and well care/reassurance/follow-up). The decreased rates observed for the remaining ten MAEs (abdominal pain, acute gastroenteritis, conjunctivitis, cough, diarrhea, febrile illness, otitis media, pharyngitis, tonsillitis, and viral syndrome) were considered to have a possible biological association with FluMist (i.e., the decreased risk may have represented FluMist-induced protection against wild-type influenza).

Table 3
MAEs with Significantly Decreased Risk

MAE	Setting
Abdominal Pain	Clinic and Combined
Acute Gastroenteritis	Clinic and Combined
ADD	Clinic
Behavioral Disorder	Clinic
Conjunctivitis	Clinic and Combined
Constipation	Clinic and Combined
Contact Dermatitis	Clinic
Cough	Clinic and Combined
Diarrhea	Clinic
Eczema	Clinic
Febrile Illness	Clinic
Gingivitis	Clinic
Gynecologic Disorder	Clinic
Migraine	Clinic
Otitis Media	ED
Pharyngitis	Clinic and Combined
Thrush	Clinic
Tonsillitis	Clinic and Combined
Trauma	ED
Viral Syndrome	Clinic
Well Care/Reassurance/FU	ED

Discussion of the Individual MAEs Associated with Increased Risk in FluMist Recipients

Of the 14 individual MAEs associated with increased risk in FluMist recipients (Table 2), a biological association with receipt of FluMist was considered implausible for eight (benign lesion, elective procedure, enuresis, speech delay, UTI, seborrhea, otitis externa, and warts). The increased risks observed for the remaining six MAEs (upper respiratory infection [URI], musculoskeletal pain, asthma, abdominal pain, otitis media with effusion [OME], and adenitis/adenopathy) were considered to have a possible biological association with FluMist.

Individual MAEs

The analyses of individual MAEs associated with biologically plausible increased risk in FluMist recipients included systematic assessment based on: the number and types of analyses associated with significantly increased or decreased risk; and, in some cases, an analysis of temporal clustering in the 42 days following vaccination. These analyses were used to assess the strength of a potential cause and effect relationship between FluMist administration and the individual MAE.

URI – Upper Respiratory Infection

In all ages, settings, and doses combined, URI occurred in 8.4% (541/6473) of FluMist recipients and 9.0% (290/3216) of placebo recipients. In three of 41 separate analyses of this event, URI was associated with significantly increased risk in FluMist recipients, while in 38 analyses it was associated with neither significantly increased nor significantly decreased risk.

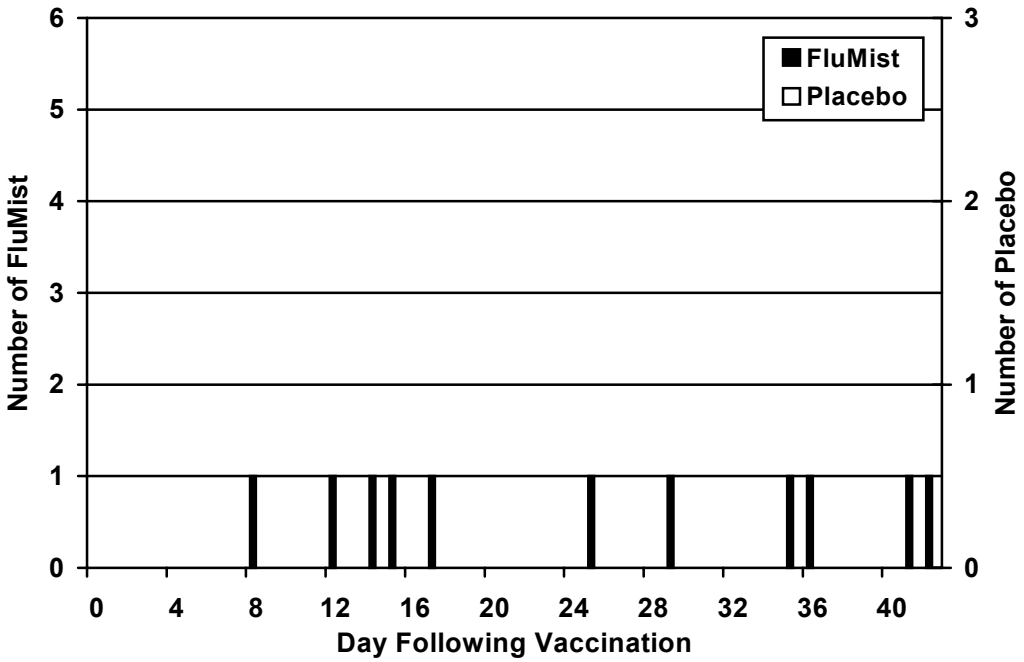
URI was associated with significantly increased risk in FluMist recipients:

- 1 to 17 years of age in the ED following Dose One
- 1 to 8 years of age in the ED following Dose One
- 18–35 months of age in all settings combined following all doses combined

Of the 831 study participants diagnosed with URI, 811 were evaluated in the clinic only (527 FluMist and 284 placebo), 17 were evaluated in the ED only (13 FluMist and 4 placebo), two were evaluated in both the clinic and the ED (one FluMist and one placebo) and one placebo recipient was hospitalized. These numbers in two treatment groups are consistent with the 2:1 randomization.

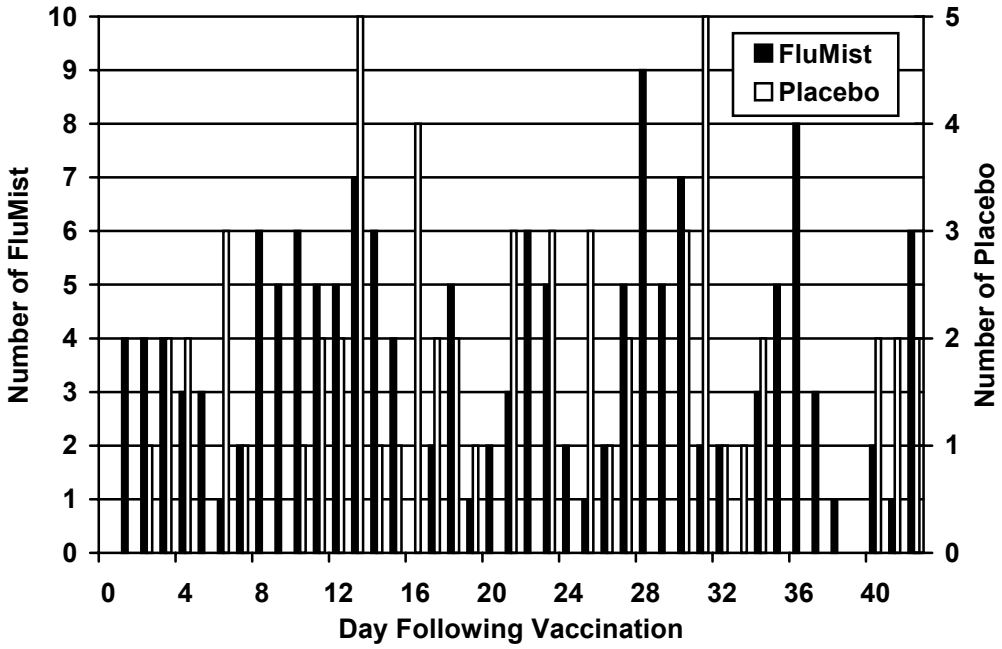
The distribution of URI events by day following Dose One for participants 1–17 years of age in the ED (Figure 1) revealed no apparent temporal clustering in FluMist recipients. No events occurred in placebo recipients in this analysis. The distribution of events following Dose One and Dose Two combined for participants 18–35 months of age in all settings combined (Figure 2) revealed limited clustering in the FluMist group in the first two weeks following vaccination. Forty percent (61/153) of the total events in FluMist recipients occurred during this interval, which represented one-third of the follow up period.

Figure 1
URI Events in the ED by Day Following Vaccination
for Participants 1–17 Years of Age,
After Dose One



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.
No events in this analysis occurred in placebo recipients.

Figure 2
URI Events in All Utilization Settings Combined by Day Following Vaccination for Participants 18–35 Months of Age, After All Doses Combined



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

The occurrence rates of URI were similar in placebo recipients compared with FluMist recipients overall. However, URI was associated with increased risk in FluMist recipients in three of 41 separate analyses of this event, and a suggestion of temporal clustering was observed in children 18–35 months of age. Therefore, a cause and effect relationship for receipt of FluMist in this study and URI cannot be excluded.

Musculoskeletal Pain

In all ages, settings, and doses combined, musculoskeletal pain occurred in 1.7% (108/6473) of FluMist recipients and 1.6% (53/3216) of placebo recipients. In two of 16 separate analyses of this event, musculoskeletal pain was associated with significantly increased risk in FluMist recipients, while in 14 analyses it was associated with neither significantly increased nor significantly decreased risk.

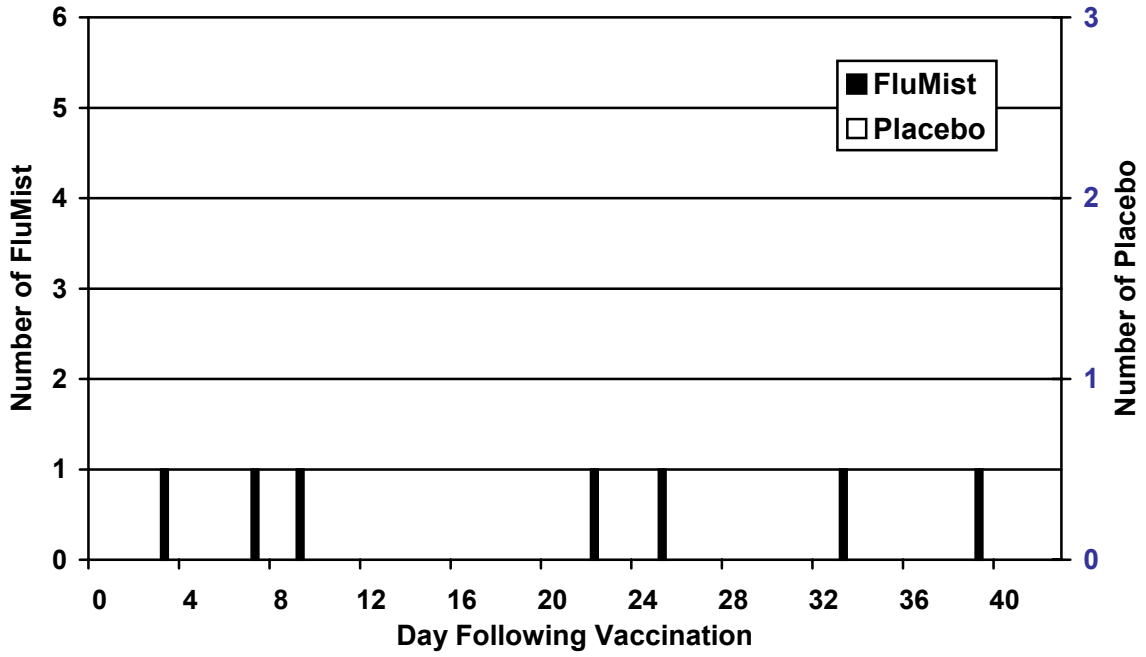
Musculoskeletal pain was associated with significantly increased risk in FluMist recipients:

- 18–35 months of age in the Clinic following Dose One
- 18–35 months of age in the Clinic following all doses combined.

Among the 161 participants with musculoskeletal pain in this study, 155 were evaluated in the clinic (103 in FluMist and 52 in placebo) and six were evaluated in the ED (five FluMist, one placebo). No hospitalizations for musculoskeletal pain occurred during the study period in FluMist or placebo recipients.

The distribution of the musculoskeletal pain events that occurred in children 18–35 months of age by day following vaccination in the clinic following all doses combined for FluMist recipients is shown in Figure 3 and revealed no apparent temporal clustering in the 42 days following vaccination. No events occurred in placebo recipients in this analysis.

Figure 3
Musculoskeletal Pain Events in the Clinic by Day Following Vaccination for Participants 18–35 Months of Age, After All Doses Combined



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio. No events in this analysis occurred in placebo recipients.

The occurrence rates of musculoskeletal pain were similar in placebo recipients compared with FluMist recipients overall. However, musculoskeletal pain was associated with increased risk in FluMist recipients in two of 16 separate analyses of this event. Therefore, a cause and effect relationship with FluMist cannot be excluded. Musculoskeletal pain events occurred in an even distribution throughout the 42 days following vaccination, and thus temporal clustering was not seen.

Asthma

In all ages, settings, and doses combined, asthma occurred in 0.9% (58/6473) of FluMist recipients and 0.9% (30/3216) of placebo recipients. In four of 31 separate analyses of this event, asthma was associated with a significantly increased risk, while in 27 analyses asthma was associated with neither significantly increased nor significantly decreased risk.

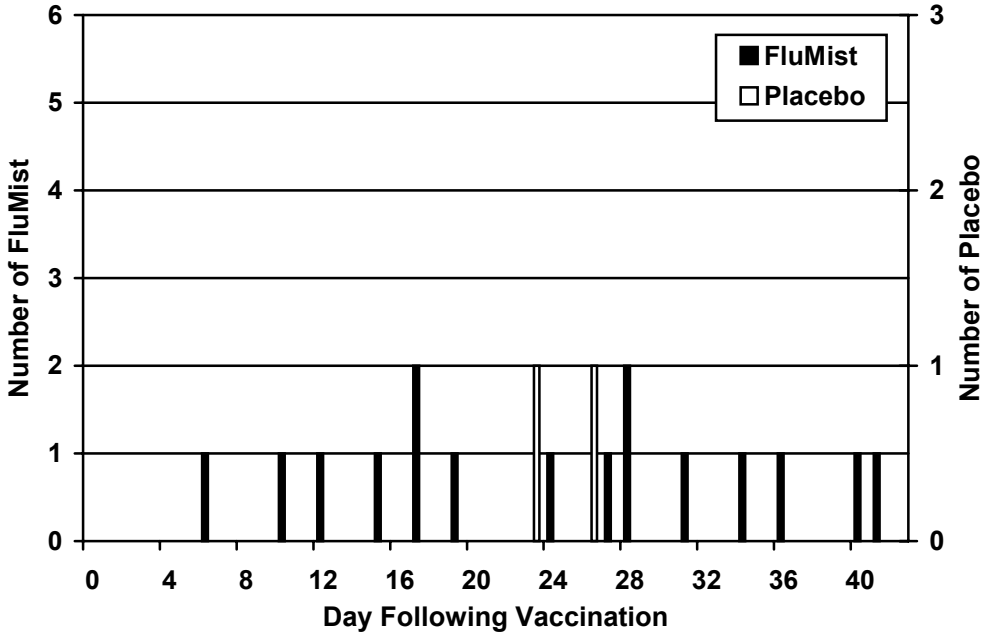
Asthma was associated with significantly increased risk in FluMist recipients:

- 18–35 months of age only:
    - in the Clinic following Dose One
    - in the Clinic following all doses combined
    - in all utilization settings combined following Dose One
    - in all utilization settings combined following all doses combined

Of the 18 asthma events (16 in FluMist, 2 in placebo) that occurred in this age group, 17 were clinic events and one event in a FluMist recipient occurred in the ED. As a result, the statistical significance associated with the "all utilization settings combined" analyses is accounted for by the significant difference in clinic events and is not indicative of asthma events occurring in other settings. No hospitalizations for asthma occurred in FluMist or placebo recipients.

The distribution of asthma events in all settings combined by day following vaccination for participants 18–35 months of age after all doses combined is shown in Figure 4. Although more asthma events occurred in the FluMist group compared with the placebo group, there was no apparent temporal clustering and no peak interval at which these events occurred.

Figure 4
Asthma in All Settings Combined by Day Following Vaccination for Participants 18–35 Months of Age, All Doses Combined



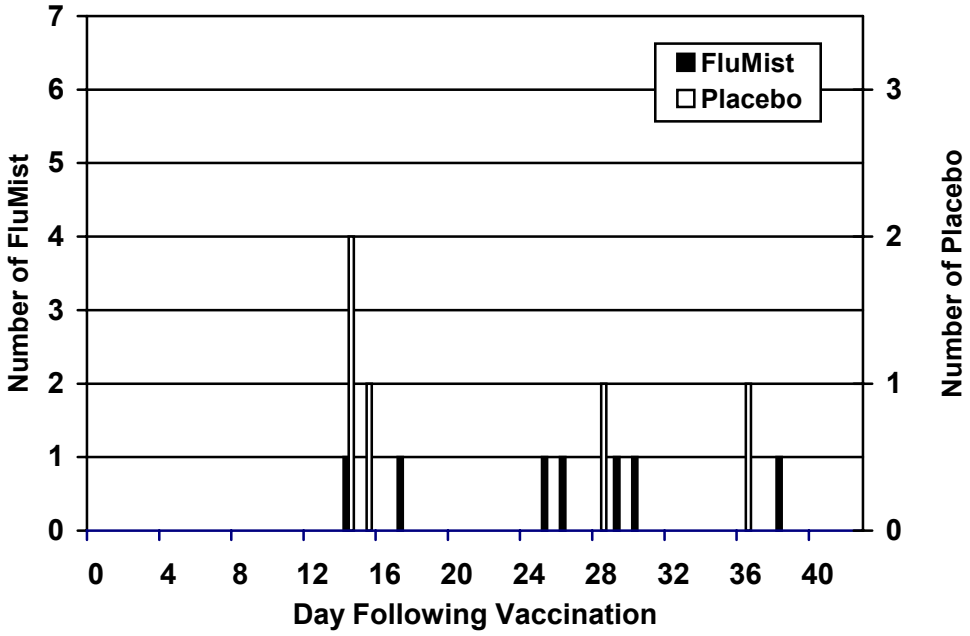
Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

An increase in asthma was not observed for FluMist recipients 12–17 months of age (n=261) in this study.

Furthermore, relying on a coded diagnosis of asthma to detect wheezing illness in young children may underestimate the event rate. Therefore, rates of wheezing/shortness of breath were also evaluated, and these diagnoses were not significantly increased in FluMist recipients in 28 separate analyses of these events, including children 18–35 months of age in the analysis of all doses and all utilization settings combined.

The distribution of wheezing/shortness of breath events in participants 18–35 months of age by day following vaccination (Figure 5) revealed no apparent temporal clustering and no consistent interval at which these events occurred.

Figure 5
Wheezing/Shortness of Breath Events in All Settings Combined by Day Following Vaccination for Participants 18–35 Months of Age, After All Doses Combined



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

In summary, the occurrence rates of asthma were similar in placebo recipients compared with FluMist recipients overall. However, asthma was associated with increased risk in FluMist recipients in four of 31 protocol-specified analyses of this event in children 18 to 35 months of age (particularly those with a past history of asthma). Therefore, a cause and effect relationship in this age group cannot be excluded. No temporal clustering of asthma was seen, however, and no increased risk of the closely related diagnosis wheezing/shortness of breath was observed.

Abdominal Pain

In all ages, settings, and doses combined, abdominal pain occurred in 0.7% (47/6473) of FluMist recipients and 0.8% (26/3216) of placebo recipients. In two of 26 separate analyses of this event, abdominal pain was associated with significantly increased risk in FluMist recipients, while in two analyses it was associated with significantly decreased risk, and in 22 analyses it was associated with neither significantly increased nor significantly decreased risk.

Abdominal pain was associated with significantly increased risk in FluMist recipients:

- 1–17 years of age in the ED following all doses combined.
- 9–17 years of age in the ED.

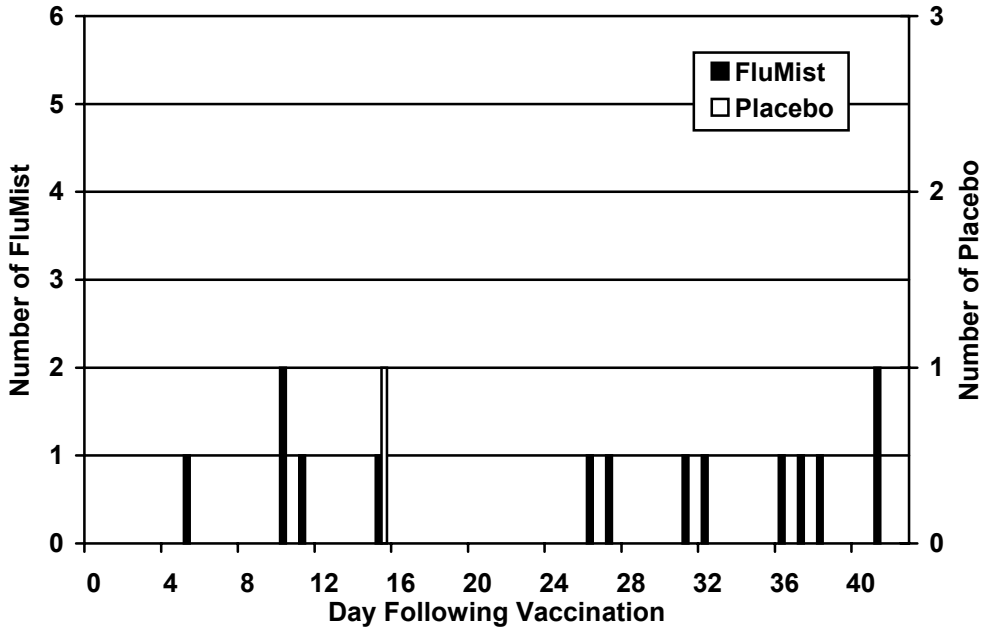
Abdominal pain was associated with significantly decreased risk in FluMist recipients:

- 1–8 years of age in the Clinic following Dose One.
- 1–8 years of age in all settings combined following Dose One.

In the analyses of abdominal pain in all settings combined and after all doses combined, no significant increases were seen in children 1–8 years of age, 9–17 years of age, or 1–17 years of age, indicating that the occurrence of abdominal pain events was not increased in FluMist recipients overall compared with placebo recipients, and that the increases noted above were specific for the ED setting. No hospitalizations for the MAE abdominal pain occurred during the study period.

The distribution of abdominal pain events by day following vaccination is shown in Figure 6 for children 1–17 years of age in the ED following all doses combined. No apparent temporal clustering of abdominal pain events was observed, and there was no consistent interval following FluMist administration at which these events occurred.

Figure 6
Abdominal Pain Events in the ED by Day Following Vaccination for Participants 1–17 Years of Age, All Doses Combined



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

The abdominal pain events analyzed above represented nonspecific pain for which an etiology was not identified by the clinician. To determine if specific abdominal disorders typically associated with abdominal pain were associated with increased risk in FluMist participants, rates of ten separate diagnostic categories, including intussusception, were analyzed among all participants (Table 4). Only appendicitis/appendiceal abscess (one event in a FluMist recipient), appendectomy for rule-out appendicitis (one event in FluMist), and acute gastroenteritis (78 events in FluMist, 47 in placebo) occurred, and these were proportionately distributed between treatment groups, considering the 2:1 randomization. No events were observed in the seven other diagnostic categories.

Table 4
Occurrence of Specific Abdominal Disorders Typically Associated with Abdominal Pain, All Settings Combined, Participants 1–17 Years of Age, All Doses Combined

Diagnosis	FluMist (N=6473) n (%)	Placebo (N=3216) n (%)
Appendicitis/Appendiceal Abscess	1[a] (0.02)	0 (0)
Appendectomy for Rule-Out Appendicitis	1[b] (0.02)	0 (0)
Acute Gastroenteritis[c]	78 (1.21)	47 (1.46)
Intestinal Obstruction	0 (0)	0 (0)
Mesenteric Adenitis	0 (0)	0 (0)
Pancreatitis	0 (0)	0 (0)
Intestinal Perforation	0 (0)	0 (0)
Ulcer	0 (0)	0 (0)
Volvulus	0 (0)	0 (0)
Intussusception	0 (0)	0 (0)

[a] Onset of symptoms pre-dated FluMist administration.

[b] No significant inflammation of the appendix by histopathological examination.

[c] Relative risk for FluMist recipients, ages 1–17 years, combined settings, combined doses: 0.82 (90% CI: 0.61, 1.12).

In summary, the occurrence rates of abdominal pain were similar in placebo recipients compared with FluMist recipients overall. Of 26 separate analyses of this event, abdominal pain was associated with increased risk in FluMist recipients in two analyses and with decreased risk for FluMist recipients in two analyses. In the remaining 22 analyses, the risk for abdominal pain was neither significantly increased nor significantly decreased for FluMist recipients. Specific, serious abdominal disorders that are frequently associated with abdominal pain were not increased in FluMist recipients. While a biologically plausible relationship between abdominal pain and FluMist may exist, the variable increased and decreased risk and lack of temporal clustering indicate that a cause and effect relationship for receipt of FluMist in this study and abdominal pain appears unlikely.

Otitis Media with Effusion (OME)

OME is a chronic condition and is not indicative of an acute process such as acute otitis media (AOM).

In all ages, settings, and doses combined, OME occurred in 1.1% (74/6473) of FluMist recipients and 1.0% (31/3216) of placebo recipients. In one of 15 separate analyses of this event, OME was associated with significantly increased risk for FluMist recipients, while in 14 analyses it was associated with neither significantly increased nor significantly decreased risk.

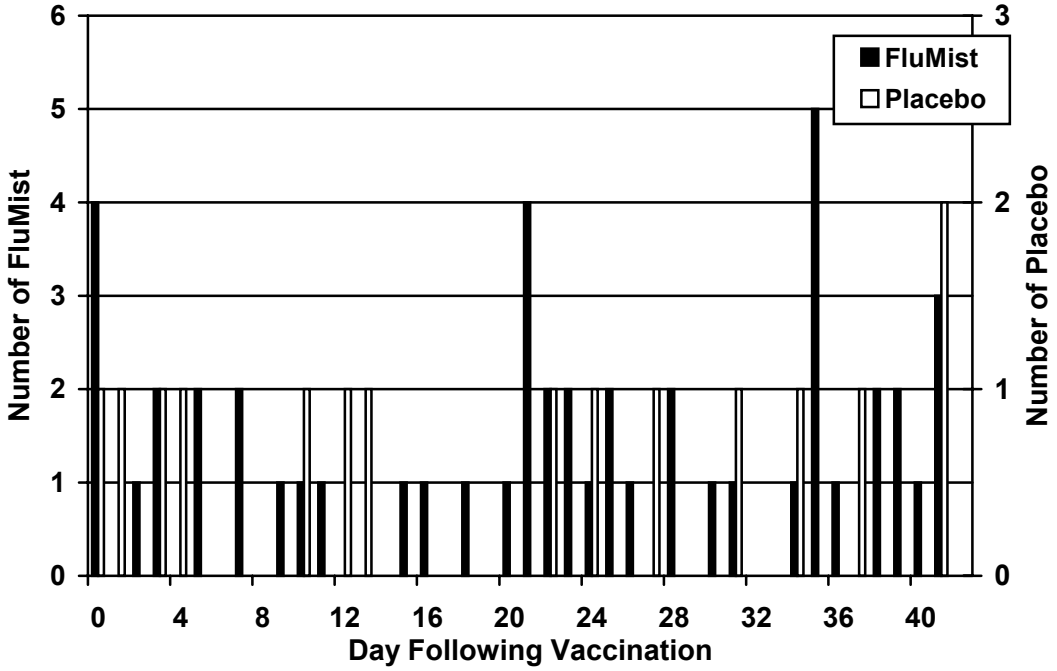
OME was associated with significantly increased risk in FluMist recipients:

- 1–8 years of age in the outpatient clinic following Dose Two

Of the 105 study participants diagnosed with OME, 104 were evaluated in the clinic (74 in FluMist and 30 in placebo), and one participant, who received placebo, was evaluated in the ED. No hospitalizations for OME occurred during the study period in FluMist or placebo recipients.

The distribution of OME events by day following vaccination is shown in Figure 7 for children 1–8 years of age in the clinic following Dose Two and revealed no apparent temporal clustering in FluMist recipients in the 42 days following vaccination.

Figure 7
OME Events in the Clinic by Day Following Vaccination
for Participants 1–8 Years of Age, After Dose Two



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

In summary, the occurrence rates of OME were similar in placebo recipients compared with FluMist recipients overall. OME was associated with increased risk in FluMist recipients in only one of 15 separate analyses of this event, after Dose Two. While a biologically plausible association between receipt of FluMist and OME may exist, temporal clustering was not observed. Definitive conclusions cannot be made from these data, but a cause and effect relationship between receipt of FluMist in this study and OME appears unlikely.

Adenitis/Adenopathy

In all ages, settings, and doses combined, adenitis/adenopathy occurred in 0.2% (16/6473) of FluMist recipients and 0.1% (4/3216) of placebo recipients. In one of eight separate analyses of this event, adenitis/adenopathy was associated with significantly increased risk in FluMist recipients,while in seven analyses it was associated with neither significantly increased nor significantly decreased risk.

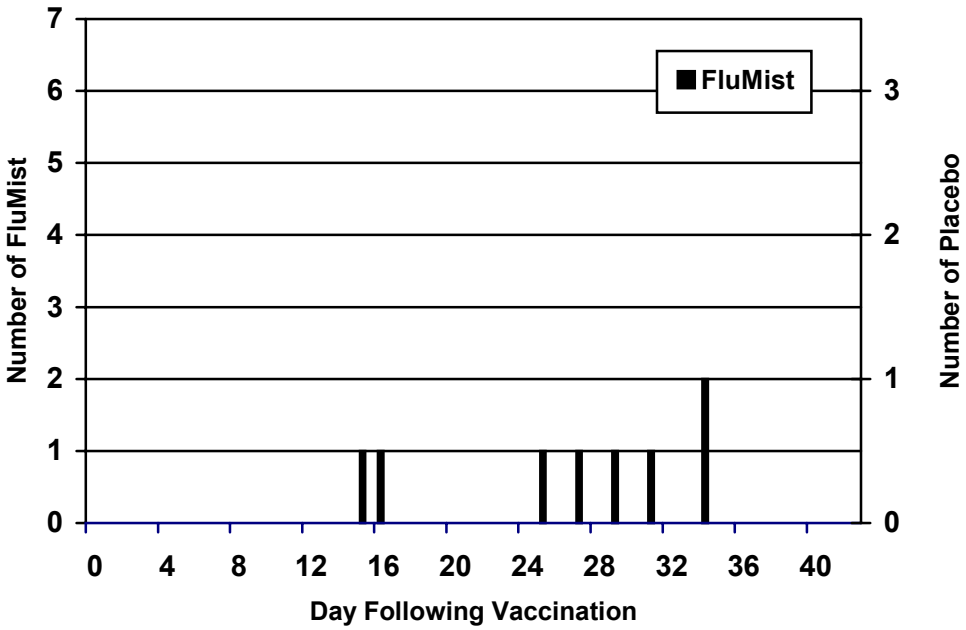
Adenitis/adenopathy was associated with significantly increased risk in FluMist recipients:

- 9–17 years of age in the clinic

All 20 participants with adenitis/adenopathy in this study were evaluated in the clinic. No hospitalizations or ED visits for adenitis/adenopathy occurred in FluMist or placebo recipients.

The distribution of the eight adenitis/adenopathy events by day following vaccination is shown in Figure 8 for participants 9–17 years of age in the clinic and revealed no apparent temporal clustering and no consistent interval at which these events occurred. All events in this analysis occurred in FluMist recipients.

Figure 8
Adenitis/Adenopathy Events in the Clinic by Day Following Vaccination for Participants 9–17 Years of Age



Note: Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio. No events in this analysis occurred in placebo recipients.

Based on medical record review of these eight events, three participants had adenitis/adenopathy prior to receipt of study vaccine (one each in the anterior chest, cervical, and buccal regions) and were evaluated on Days 16, 31, and 34 after vaccination, respectively. Two participants had cervical adenopathy secondary to identified processes (acute varicella infection diagnosed on Day 25, and a pustule on the chin on Day 15). Of the three remaining

participants, each of whom had cervical adenopathy, two had mononucleosis-like illness (Days 27 and 34, respectively) and one had chronic upper respiratory allergic symptoms (Day 29).

In summary, the occurrence rates of adenitis/adenopathy were similar in placebo recipients compared with FluMist recipients overall. Adenitis/adenopathy was associated with increased risk in one of eight separate analyses of this event. While a biologically plausible relationship between adenitis/adenopathy and FluMist may exist, increased risk was seen in only one analysis, most of the events were attributable to factors other than vaccination, and temporal clustering was not observed. A cause and effect relationship for receipt of FluMist in this study and adenitis/adenopathy appears unlikely.

Overall SAEs

SAEs were collected for the 42-day period following each FluMist or placebo administration. SAEs occurred at a rate of 0.2% and were proportionately distributed between FluMist (N=13) and placebo (N=7). Eleven SAEs were hospitalizations for acute medical processes (in FluMist recipients, acute gastroenteritis, appendicitis/appendiceal abscess, appendectomy for rule-out appendicitis, gynecologic disorder/abdominal pain, hemolytic uremic syndrome, testicular torsion, and upper airway obstruction post-extubation for tonsillectomy; in placebo recipients, cellulitis/fractured clavicle, croup, dehydration, and diabetes), six SAEs were psychiatric hospitalizations (four in FluMist recipients, two in placebo recipients), and the remaining three SAEs included one ED visit for trauma in a placebo recipient, one elective surgery for a benign lesion of the foot in a FluMist recipient, and one outpatient diagnosis of synovial sarcoma in a FluMist recipient.

No SAEs in the FluMist recipients were judged related to study vaccine. Of the 93 participants who left the KP health plan during the study period, 55 were able to be contacted; no SAEs were identified in these participants by parent/guardian report.

No deaths occurred among the study participants.

CONCLUSIONS

This trial in which 6,473 participants 1–17 years of age were vaccinated with FluMist showed that FluMist was generally safe and well-tolerated in healthy children and adolescents.

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Table 1
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 225

Month/ Year	Day of Month	1076		1078		1079		1093		1169		1170		1172	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
January 2000	4	**P**		**P**		**V**		**V**							
		n	n	n	n	n	n	n	n						
	5	**WT**	n	n	n	**VT**	**ND**	**?**	**ND**						
	6														
	7	**WT**	n	n	n	n	**VT**	**VT**	**ND**						
	8														
	9														
	10			n	n	**VT**	**ND**	**?**	**VT**						
	11														
	2			n	n	**VT**	**VT**	n	n						
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	22														
	23									n	n	n	n	n	n
	24									n	n	n	n	n	n

Legend: n = none detected, P= Placebo dosed, V= CAIV-T dosed, VT = vaccine type detected, ND= detected not typed, ? = detected unable to subtype
A= Type A influenza, B= Type B Inlfuenza

Table 2
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 107

Month/ Year	Day of Month	1085		1086		1089		**1090**		1108	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
January 2000	11	**V**		**P**		**V**		**P**			
		n	n	n	n	n	n	n	n		
	12	**?**	n	n	n	n	n	n	n		
	13									**V**	
										n	n
	14	**VT**	**ND**	n	n	n	**VT**	n	n	n	**ND**
	15										
	16										
	17	n	n	n	n	n	n	n	n	n	**VT**
	18										
	19	n	**VT**	n	n	n	n	n	n	n	n
	20										
	21	n	n	n	n	n	n	n	n	n	n
	22										
	23										
	24	n	n	n	n	n	n	n	n	n	n
	25										
	26	n	n	n	n	n	n	n	n	n	n
	27										
	28	n	n	n	n	n	n	n	n	n	n
	29										
	30										
	31	n	n	n	n	n	n	**WT**	n	n	n
February 2000	1	n	n			n	n	**WT**	n		
	2									n	n
	3			n	n					n	n

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza

Table 3
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 250

Month/ Year	Day of Month	1197		1198		1201		1203		1204	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
February 2000	15	**P**		**P**							
		n	n	n	n						
	16	n	n	n	n						
	17					**P**		**V**		**V**	
						n	n	n	n	n	n
	18	n	n	n	n	n	n	**VT**	n	n	**ND**
	19										
	20										
	21	n	n	n	n	n	n	n	**ND**		
	22										
	23	n	n			n	n	n	**ND**	n	n
	24										
	25	n	n	n	n	n	n	n	**VT**	n	**VT**
	26										
	27										
	28	n	n	n	n	n	n	n	n	n	n
	29	n	n	n	n	n	n	n	n	n	n
March 2000	1	n	**VT**	n	n	n	n	n	n	n	n
	2										
	3	n	n	n	n	n	n	n	n	n	n
	4										
	5										
	6	n	n	n	n	n	n	n	n	n	n
	7	n	n	n	n						
	8					n	n	n	n	n	n
	9					n	n	n	n	n	n

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza

Table 4
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 219

Month/ Year	Day of Month	1016		1019		1021		1023		**1028**	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
November 1999	16	**P**		**P**		**V**					
		n	n	n	n	n	n				
	17	n	n	n	n	**VT**	**ND**				
	18							**V**		**P**	
								n	n	n	n
	19	n	n	n	n	**VT**	**ND**	n	n	n	n
	20										
	21										
	22	n	n	n	n	n	**ND**	n	**ND**	n	n
	23										
	24	n	n	n	n	n	**ND**	n	**ND**		
	25										
	26	n	n	n	n	n	**VT**	n	**VT**	**?**	n
	27										
	28										
	29	n	n	n	n	n	n	n	n	n	n
	30										
December 1999	1	n	n	n	n	n	n	n	n		
	2										
	3	n	n	n	n	n	n	n	n	n	n
	4										
	5										
	6										
	7	n	n	n	n	n	n	n	n	n	n
	8							n	n	n	n
	9							n	n	n	n
	10										
	11										
	12										
	13										
	14									n	n

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza

Table 5
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 205

Month/ Year	Day of Month	1040		1033		1047		1048	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
November 1999	23	**P**		**P**					
		?	n	n	n				
	24	n	n	n	n				
	25					**P**		**V**	
						n	n	n	n
	26	n	n	n	n	n	n	n	n
	27								
	28								
	29	n	n	n	n	n	n	**VT**	n
	30								
December 1999	1	n	n	n	n	n	n	**VT**	n
	2								
	3	n	n	n	n	n	n	**VT**	n
	4								
	5								
	6								
	7	n	n	n	n			n	n
	8	n	n	n	n			n	n
	9								
	10	n	n	n	n			n	n
	11								
	12								
	13	n	n	n	n			n	n
	14			n	n				
	15							n	n
	16	n	n			n	n	n	n

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza

Table 6
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 201

Month/ Year	Day of Month	1026		1032		1036		1038		1042	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
November 1999	18	**P**									
		?	n								
	19	n	n								
	20										
	21										
	22	n	n								
	23			**V**		**V**		**V**		**P**	
				n	n	n	n	**?**	**N**	n	n
	24	**?**	n	n	n	**VT**	**ND**	**VT**	**ND**	n	n
	25										
	26	n	n	n	n	n	**ND**	**?**	**ND**	n	n
	27										
	28										
	29	n	n	n	**VT**	n	**VT**	n	**ND**	n	n
	30										
December 1999	1	n	n	n	n	n	n	n	**ND**	n	n
	2										
	3	n	n	n	n	n	n	n	**VT**	n	n
	4										
	5										
	6										
	7	n	n	n	n	n	n	n	n	n	n
	8	n	n	n	n	n	n	n	n	n	n
	9	n	n								
	10			n	n	n	n	n	n	n	n
	11										
	12										
	13			n	n	n	n	n	n	n	n
	14			n	n	n	n	**VT**	n	n	n

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza

Table 7
Composition of the Playgroups of the Seven Placebo Participants Who Shed Influenza Virus in Study D145-P500 – Playgroup 101

Month/ Year	Day of Month	**1001**		1002		1003		1004		1005		1006	
		A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
November 1999	16	**P**		**P**		**V**		**P**					
		n	n	n	n	n	n	n	n				
	17	n	n	n	n	n	n	n	n				
	18									**V**		**P**	
										n	n	n	n
	19	n	n	n	n	n	n			n	n	n	n
	20												
	21												
	22	n	n	n	n	n	n	n	n	n	n	n	n
	23												
	24	n	n	n	n	n	n	n	n	n	n	n	n
	25												
	26	n	n	n	n	n	n	n	n	n	**VT**	n	n
	27												
	28												
	29	n	n	n	n	n	n	n	n	n	n	n	n
	30												
December 1999	1	**?**	n	n	n	n	n	n	n	n	n	n	n
	2												
	3	n	n	n	n	n	n	n	n	n	n	n	n
	4												
	5												
	6												
	7	n	n	n	n	n	n	n	n	n	n	n	n
	8									n	n	n	n
	9									n	n		
	10												
	11												
	12												
	13											n	n
	14												

Legend
n = none detected
P = Placebo dosed
V = CAIV-T dosed
VT = vaccine type detected
ND = detected not typed
? = detected unable to subtype

A=Type A Influenza, B= Type B Influenza